Screening Asymptomatic Diabetic Patients for Coronary Artery Disease

Why Not?
Todd D. Miller, MD, FACC,* Rita F. Redberg, MD, MSc, FACC,† Frans J. T. Wackers, MD, FACC‡
Rochester, Minnesota; San Francisco, California; and New Haven, Connecticut

Given the elevated risk of cardiovascular events and the higher prevalence of silent coronary artery disease (CAD) in diabetic versus non-diabetic patients, screening asymptomatic diabetic patients for CAD is an appealing concept. However, many factors argue against implementing a broad-based screening program at the present time. Foremost is the lack of any published data demonstrating that a prospectively applied screening program improves outcome in asymptomatic diabetic patients. The true prevalence of CAD, and in particular prognostically important CAD, in this population is uncertain. Consensus documents recommend more aggressive treatment of hypertension and hyperlipidemia solely on the basis of diabetes status, without differentiation based on the presence or absence of identifiable CAD. There is no evidence that use of anti-ischemic medication can alter the natural history of CAD in these patients. Retrospectively performed studies using stress single-photon emission computed tomography (SPECT) imaging have reported that approximately 50% and 20% of patients have abnormal and high-risk images, respectively. However, the only prospectively designed study, the DIAD (Detection of Ischemia in Asymptomatic Diabetics) study, reported a much lower percentage of abnormal SPECT images (16%) and images with a very large (≥10% of the left ventricle) defect (1%). The financial implications of screening all asymptomatic diabetic patients determined to be at intermediate and high risk by clinical scoring systems is enormous. Clearly more data are needed to address this issue. Future studies should consider possible methods to enrich the patient subset that might benefit from screening and should include carefully performed cost-effective analyses. (J Am Coll Cardiol 2006;48:761–4) © 2006 by the American College of Cardiology Foundation

The incidence of diabetes mellitus has increased at an alarming rate over the past 2 decades. Current estimates of the numbers of people with diabetes include 17.7 million in the U.S. and 171 million worldwide (1). These numbers are projected to double by the year 2030. The association between diabetes and cardiovascular disease is well established (2). Coronary artery disease (CAD) is the leading cause of death in diabetic patients, accounting for 75% of the deaths (3). Coronary artery disease is also more often silent in patients with diabetes (4).

Given these associations between CAD and diabetes, screening for CAD in asymptomatic diabetic patients is an appealing concept. In this issue of the Journal, Bax et al. (5) review the literature regarding the use of noninvasive imaging modalities for the screening of asymptomatic patients with diabetes. They propose more widespread use of stress single-photon emission computed tomography (SPECT) for this purpose.

REQUIREMENTS OF A SCREENING TOOL

For a screening test to be useful, selected criteria should be satisfied, including the following items.

The prevalence of disease in the population must be high enough such that a meaningful number of afflicted individuals can be identified. The true prevalence of CAD in asymptomatic patients with diabetes is unknown. Autopsy studies have reported a prevalence of CAD in decedents with diabetes but without antemortem evidence of CAD ranging from 50% to 75% (6,7). The major limitation of postmortem studies relates to referral bias (the prevalence of CAD might be very different in living subjects). As noted by Bax et al. (5), the prevalence of abnormal radionuclide myocardial perfusion images in the nuclear cardiology literature ranges between 21% and 59%. These figures indicate only positive test results and not the prevalence of anatomic CAD, because coronary angiography was not performed in all patients in these studies. This wide range of abnormal test results likely relates to differing methodologies in these studies and the enrollment of small numbers of patients in most. Two recent large retrospective studies from Cedars Sinai (n = 826) (8) and the Mayo Clinic (n = 1427) (9) reported abnormal stress SPECT images in 39% and 58% of asymptomatic diabetic patients, respectively. Retrospectively designed studies have several limitations, including selection bias of higher-risk patients. The only prospective study to use stress SPECT imaging is the DIAD (Detection of Ischemia in Asymptomatic Diabetics) study (10). In this study 1,123 asymptomatic patients with type 2 diabetes,
ages 50 to 75 years, were recruited and randomized to adenosine (with or without low-level exercise) SPECT or no imaging. In the imaging arm (n = 522), 16% had abnormal images, considerably lower than in the retrospective studies previously cited. There is no published large angiographic series in asymptomatic patients with diabetes.

The screening test must accurately characterize low- and high-risk patients. Stress SPECT is well-established for its risk stratifying properties (11). According to the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines (12), patients characterized as low risk should have an annual cardiac death rate <1%. The annual risk of cardiac death or nonfatal myocardial infarction in general patient populations with normal SPECT images is 0.6% (13). The ability of stress SPECT to identify low-risk diabetic patients might not be as accurate. In the Cedars-Sinai study (8), the annual rate of cardiac death or nonfatal myocardial infarction in asymptomatic diabetic patients with normal images was 1.6%. In the Mayo Clinic study (9), annual mortality (a breakdown into cardiac and noncardiac mortality was not possible, because only the Social Security Death Index was applied for assessing outcome) in patients categorized as low risk by SPECT was 3.6%. Follow-up data on patients enrolled in the DIAD study is not yet available. The higher-than-expected event rates in diabetic patients categorized as low risk by SPECT imaging has also been noted in general diabetic patients with stress echocardiography (14–16), questioning whether any of the commonly used stress imaging modalities can accurately identify diabetic patients who are truly at low risk (17).

Identification of individuals afflicted with the disease should lead to a treatment that improves outcome. Bax et al. (5) state, “There is a clear need to identify patients with type 2 diabetes who are at risk of cardiovascular events before the onset of symptoms.” However, they never specifically indicate how this knowledge should be applied in clinical practice. A common argument for identifying CAD in asymptomatic patients in general is to intensify treatment of risk factors. This rationale might not apply to treatment of risk factors in diabetic patients. The National Cholesterol Education Program (NCEP) (18) and Joint National Committee on Hypertension VII (19) recommend more aggressive treatment of lipids and hypertension, respectively, simply on the basis of diabetes status. As noted in the AHA Prevention Conference VI proceedings paper (20), the results of a screening test in diabetic patients do not alter risk factor management, because these patients are considered higher risk on the basis of diabetes alone. In clinical practice, beta-blockers are often prescribed to patients with silent ischemia but without evidence that they alter the natural history of chronic CAD. The goal of screening might be to identify individuals with severe CAD who are candidates for revascularization. The BARI (Bypass and Angioplasty Revascularization Intervention) trial compared outcomes in symptomatic patients (two-thirds unstable angina) with multivessel CAD randomized to coronary artery bypass grafting (CABG) or balloon angioplasty. In the diabetic subset of patients, those assigned to CABG had better survival (21). There are no randomized data comparing treatment strategies in asymptomatic diabetic patients. If the major goal of screening is to select potential candidates for revascularization, a sufficiently large number of patients with severely abnormal, not just mildly abnormal, SPECT images must be identified. In the Mayo Clinic study (9), 18% of the population had high-risk SPECT images. Follow-up of this patient subset, in whom treatment selection was at the discretion of patients and their physicians, indicated that those treated with CABG had better survival (22). It might be more difficult to detect patients with severely abnormal images prospectively. In the DIAD study (10) only 1% of the screened population had perfusion defects that measured ≥10% of the left ventricle, the threshold for defect size in general populations associated with better outcome with revascularization (23).

The process should be cost-effective. Bax et al. (5) recommend using clinical risk scores and proceeding with stress SPECT in diabetic patients categorized as intermediate or high risk. These scores are determined by age, gender, and the presence and severity of risk factors. Applying the original Framingham risk scoring (24) and the 5% adjustment to convert “total” to “hard” CAD risk recommended by the NCEP (18), all diabetic men and women who are ≥60 years old are at intermediate risk, regardless of the presence of any other risk factors. The proposal by Bax et al. (5) would result in screening all diabetic patients ≥60 years old and many younger patients with additional risk factors. Of the 17 to 18 million patients with diabetes in the U.S., approximately 20% have recognized CAD (25). The number of the remaining approximately 14 million who are intermediate or high risk by clinical assessment is not known but is likely to be substantial. Stress SPECT imaging is expensive, especially as currently performed, with add-on costs for gated left ventricular ejection fraction and wall motion measurements (total Medicare Relative Value Units 22.37 for Current Procedure Terminology codes 78465, 78478, 78480, and 93015, and additional pharmaceutical charges for the radio-
CONCLUSIONS

The detection of silent CAD in patients with diabetes will assume even greater importance as a health issue in the future as the number of people with diabetes increases. Clearly more studies are needed. Collection of follow-up data, which is currently in progress in both the DIAD and BARI-2D trials, might help clarify whether certain diabetic patients benefit from screening. Although screening on the basis of multiple risk factors seems intuitive, it is important to note that in both the DIAD (10) and Mayo Clinic (9) studies, multiple risk factors did not predict which patients had severely abnormal SPECT images. The Mayo Clinic studies (9,22) demonstrated that there is a subset of asymptomatic diabetic patients with severe CAD who can be detected by SPECT and whose outcome might be enhanced by CABG. However, the results from the DIAD study (10) suggest that the yield of detecting patients with severely abnormal images will be low when SPECT is applied in a prospective manner as the first and only test. A challenge for future studies will be to discover methods to “enrich” the screened population to pre-select patients for SPECT imaging. In the current era of escalating medical costs with an emphasis on evidence-based medicine, it is difficult to support a broad recommendation to screen all intermediate- and high-risk asymptomatic diabetic patients with stress SPECT imaging only. Until more data become available, clinicians should judiciously apply screening tests on individual asymptomatic patients on the basis of clinical judgment.

Reprint requests and correspondence: Dr. Todd D. Miller, Mayo Clinic, Gonda 5-412, 200 First Street, SW, Rochester, Minnesota 55901. E-mail: miller.todd@mayo.edu.

REFERENCES


